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THERMAL ANALYSIS OF THE DEHYDRATION PROCESS OF CROSS-LINKED POLYVINYLPYRROLIDONE AND ITS MIXTURES WITH NAPROXEN

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ABSTRACT

Ways of finding kinetic parameters useful for pharmaceutical formulators from thermal analytical methods (TGA, DSC) under both isothermal and non-isothermal conditions are suggested. We considered as an example those followed to determine the first-order kinetics of dehydration of cross-linked polyvinylpyrrolidone (PVP XL). PVP XL samples differing in particle size (granulometric fractions in the 250 μm to 63 μm range) and/or equilibrium moisture content (12 to 32 g_{H_2O}/100 g) show activation energy values in the 43 to 54 kJ mol^{-1} (non-isothermal TGA) and 48 to 61 kJ mol^{-1} (non-isothermal DSC) ranges. The weight fraction of water present may influence the activation energy of the dehydration process whilst the particle size of PVP XL seems not to affect this parameter. The low interaction energy between PVP XL and water suggests that the interaction mainly occurs within the porous agglomerates of the polymer particles, at the intraparticulate surface level (surface-type interaction). The influence of an admixed drug (naproxen) on the thermodynamic and kinetic parameters of PVP XL dehydration suggests that analogous surface phenomena are probably involved in the solid-state interaction between the amorphous polymer and the crystalline drug.

INTRODUCTION

Water combined with polymeric pharmaceutical excipients can influence physical chemical properties such as glass transition temperature, stability, powder flow, compaction, dissolution rate of solid dosage forms, etc. [1-3]. The effects of moisture depend on the amount of water which will be sorbed or desorbed at various relative humidities and temperatures, as well as on its strength of combination ("free" or "bound" water). The kinetics of water loss is therefore a valuable parameter to characterise a pharmaceutical excipient. Moreover, the possible influence of an admixed drug on dehydration kinetics gives useful information on both the polymer-water-drug interactions in pharmaceutical formulations and the performance of the excipient in the development of solid dosage forms. Cross-linked polyvinylpyrrolidone (PVP XL) is an insoluble

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homopolymer of N-vinyl-2-pyrrolidone which ideally seems to fulfil all the requirements of a real tablet super-disintegrant [4]. The hydration capacity, maximum moisture sorption, and dehydration kinetics of PVP XL are known [5,6]. This study is a contribution to the understanding of PVP XL solid-state interactions with water when a crystalline drug, more precisely (*S*)-6-methoxy-α-methyl-2-naphtaleneacetic acid or naproxen, is also present. The influence of particle size, water content and system composition on the kinetics of water loss of the polymer has been determined through thermal analytical methods, in particular thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

MATERIALS AND METHODS

Materials - PVP XL (Polyplasdone-XL, GAF, Italy) of commercial grade was sieved and the 60-80 mesh (250-180 μm), 80-120 mesh (180-125 μm), and 120-230 mesh (125-63 μm) granulometric fractions were collected. The particle size distribution was assessed with a Coulter Counter (Fig. 1). (*S*)-6-Methoxy-α-methyl-2-naphtaleneacetic acid (naproxen, NAP) (Sigma, USA) of commercial grade was sieved and the 120-230 mesh (125-63 μm) granulometric fraction was selected. Other used chemicals were of analytical grade.

Preparation of Samples - Relative humidity (RH) chambers were prepared using saturated solutions of CrO_3 (40% RH), $Na_2Cr_2O_7$ (54% RH), NaCl (75% RH), and K_2SO_4 (97% RH) in glass cabinets at controlled room temperature (25 °C±2 °C) [7]. Samples were equilibrated for 7 days below these moisture conditions. The equilibrium moisture content (EMC) of PVP XL samples kept for 7 days at 25 °C±2 °C and at constant RH conditions, was determined by TGA. Blends of NAP (125-63 μm granulometric fraction) and PVP XL (125-63 μm granulometric fraction equilibrated at 40% RH, water content 11.9% by weight) in the range 10% to 90% by weight of NAP were tested. Samples of about 2.000 mg of PVP XL and proportional amounts of NAP were prepared directly in DSC pans sealed with pierced lids.

Thermal Analysis - Thermogravimetric analysis was conducted on a Mettler TG50 apparatus (10 K min^{-1}, 25-150 °C) on 9-10 mg samples in alumina crucibles under a nitrogen atmosphere (30 ml min^{-1}). Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus equipped with a 25 mod. DSC cell (10 K min^{-1} ; 25-175 °C) on 7-10 mg samples in pierced Al pans (Mettler M3 microbalance) under static air. The kinetic parameters were calculated from both TGA and DSC experiments using the built-in software programmes "TG KINETIC" and "DSC KINETIC".

THEORETICAL DEVELOPMENT

There are several methods of obtaining kinetic data from TGA or DSC curves. Not all kinetic approaches are equally reliable and no single method is satisfactory for all reactions. However an isothermal run is an absolute requirement to confirm the findings of results obtained by dynamic methodologies. To facilitate understanding, we report here the approach followed by Margheritis et al. [6] to determine the dehydration kinetics of commercial PVP XL (water content about 10% by weight), since it is of great potential interest to the pharmaceutical formulator.

The kinetic equation involves a function, $f(\alpha)$, and its integrated form, $g(\alpha)$, where α is the fraction of dehydrated PVP XL at time t. The rate of dehydration is expressed in a general way by:

$$d\alpha/dt = K(T)\, f(\alpha), \qquad (1)$$

where K(T) is the rate constant that depends on the absolute temperature T according to the Arrhenius equation:

$$K(T) = A \exp(-E_{act}/RT). \qquad (2)$$

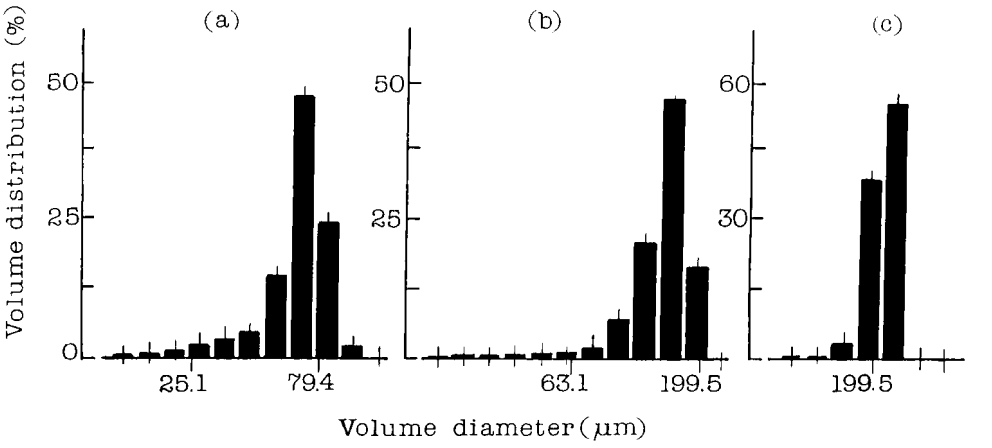

FIGURE 1
Particle size distribution (Coulter Counter) of cross-linked polyvinylpyrrolidone (PVP XL): sieve granulometric fractions 125-63 μm (a), 180-125 μm (b), 250-180 μm (c).

A is the preexponential Arrhenius factor, E_{act} the activation energy of dehydration, and R the gas constant. When the analytical form of the $f(\alpha)$ function is known, Eq. (1) can be integrated at constant temperature as follows:

$$g(\alpha) = \int_0^{\alpha} d\alpha/f(\alpha) = K(T)\, t. \quad (3)$$

For PVP XL, curves were constructed from the isothermal gravimetry data at 26, 31, 36, and 39 °C, respectively, by plotting α *vs* time t (Fig. 2a). Examination of conformity to Eq. (3) proposed for various types of solid-state decomposition was carried out by plotting the calculated values of $g(\alpha)$ in Table 1 [8,9] *vs* t. The integrated form of the function $f(\alpha)$ which best fits the experimental data was found to be (Fig. 2b):

$$g(\alpha) = -\ln(1-\alpha). \quad (4)$$

Thus PVP XL dehydration conformed at every temperature to a first-order kinetics. The activation energy evaluated from the Arrhenius plot (Fig. 2c) was 67.4 kJ mol^{-1}.

Under non-isothermal conditions, the sample temperature changes linearly with time. For a linear heating rate, *e.g.* q K min^{-1}:

$$q = dT/dt. \quad (5)$$

Combining Eqs. (1), (2), (5), rearranging and integrating we get:

$$\int_0^{\alpha} d\alpha/f(\alpha) = (A/q) \int_{T_0}^{T} \exp(-E_{act}/RT)\, dT. \quad (6)$$

The right-hand side of Eq. (6) does not have an exact integral but it can be integrated by making mathematical approximations according to the so-called "integral" methods (see for example ref. [10]). The integration can be avoided following a so-called "differential" method, for example that of Achar, Brindley and Sharp [11]. It is based on

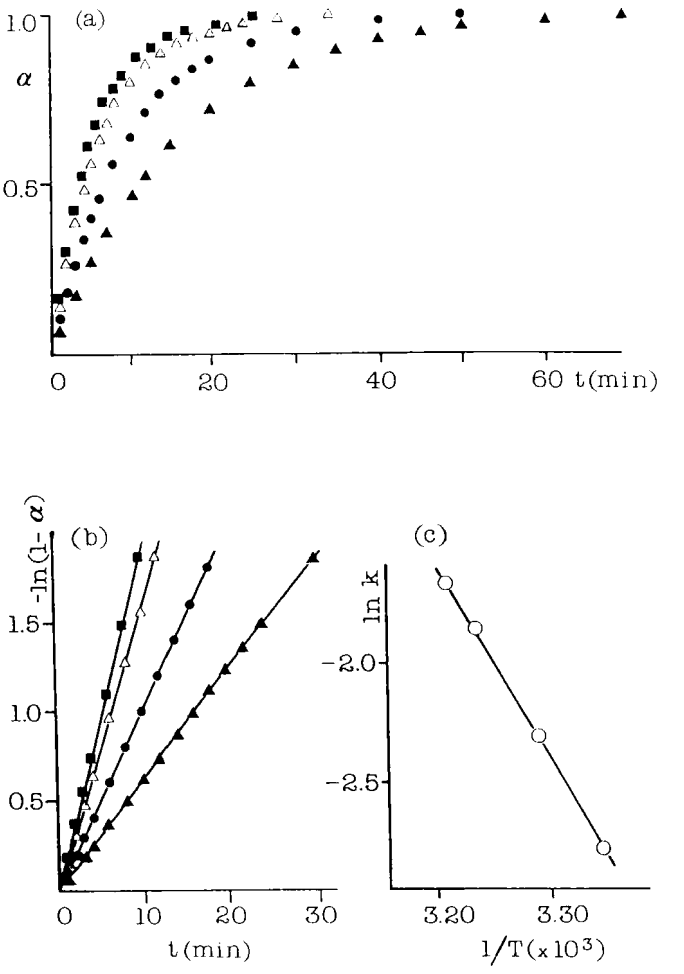

FIGURE 2
Dehydration kinetics of PVP XL: (a) dehydrated fraction α as a function of time at 26 °C (▲), 31 °C (●), 36 °C (△), 39 °C (■); (b) integrated form ($g(\alpha)$ = - ln(1-α)) of $f(\alpha)$ which best fits the experimental data; (c) Arrhenius plot (Eq. (2)).

TABLE 1
Kinetic Equations for the Most Common Mechanisms Believed to Operate in Solid-State Decomposition.

Function of the fraction decomposed at time t, $f(\alpha)$	Integrated form of $f(\alpha)$, $g(\alpha)$	Mechanism
1	α	Zero-order mechanism. (Polany-Wigner equation)
$(1-\alpha)^{1/2}$	$2[1-(1-\alpha)^{1/2}]$	One-half order mechanism. Phase boundary reaction; cylindrical symmetry.
$(1-\alpha)^{2/3}$	$3[1-(1-\alpha)^{1/3}]$	Two-thirds order mechanism. Phase boundary reaction; spherical symmetry.
$(1-\alpha)$	$-\ln(1-\alpha)$	First-order mechanism. Random nucleation, one nucleus on each particle.
$2[-\ln(1-\alpha)^{1/2}](1-\alpha)$	$[-\ln(1-\alpha)]^{1/2}$	Random nucleation, two-dimensional growth of nuclei. (Avrami-Erofeev equation)
$3[-\ln(1-\alpha)^{2/3}](1-\alpha)$	$[-\ln(1-\alpha)]^{1/3}$	Random nucleation, three-dimensional growth of nuclei. (Avrami-Erofeev equation)
$1/(2\alpha)$	α^2	One-dimensional diffusion.
$1/[-\ln(1-\alpha)]$	$(1-\alpha)\ln(1-\alpha) + \alpha$	Two-dimensional diffusion.
$3(1-\alpha)^{2/3}/2[1-(1-\alpha)^{1/3}]$	$[1-(1-\alpha)^{1/3}]^2$	Three-dimensional diffusion. (Jander equation)
$3/2[(1-\alpha)^{-1/3} -1]$	$(1-2\alpha/3)-(1-\alpha)^{2/3}$	Three-dimensional diffusion. (Ginsting-Brounshtein equation)

the general differential equation for reactions following "n order" kinetics:

$$d\alpha/dT = (A/q)\exp(-E_{act}/RT)(1-\alpha)^n, \quad (7)$$

which is obtained combining Eqs. (1), (2), and (5), and putting $f(\alpha) = (1-\alpha)^n$, n being the order of reaction. Rearranging and taking logs, we have:

$$\ln[d\alpha/(1-\alpha)^n dT] = \ln(A/q) - E_{act}/RT. \quad (8)$$

By plotting the fraction of dehydrated PVP XL (α) obtained from dynamic TGA measurements at differing heating rates as a function of absolute temperature, $d\alpha/dT$ values can be obtained and the respective left-hand side values of Eq. (8) can be calculated for the possible n values of solid-state reactions. Then the left-hand side values of Eq. (8) can be plotted *vs* 1/T. For PVP XL, linear relationships were obtained only for n = 1 (first-order reaction) at both the heating rates tested (Fig. 3a). The activation

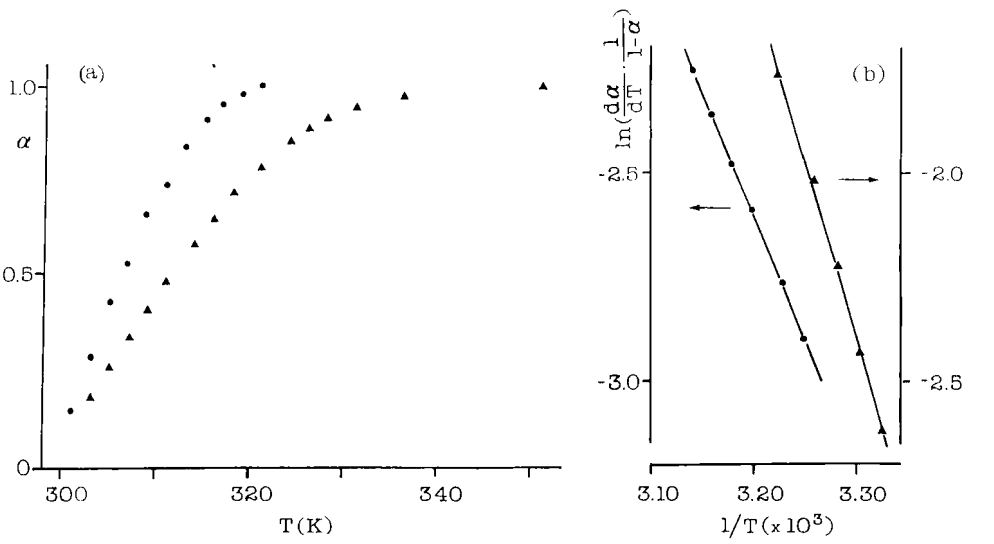

FIGURE 3
Dehydration kinetics of PVP XL: (a) dehydrated fraction α as a function of T at 1 (●) and 2 (▲) K min^{-1}; (b) plot of the left-hand side values of Eq. (8) for n =1 *vs* 1/T at 1 and 2 K min^{-1}.

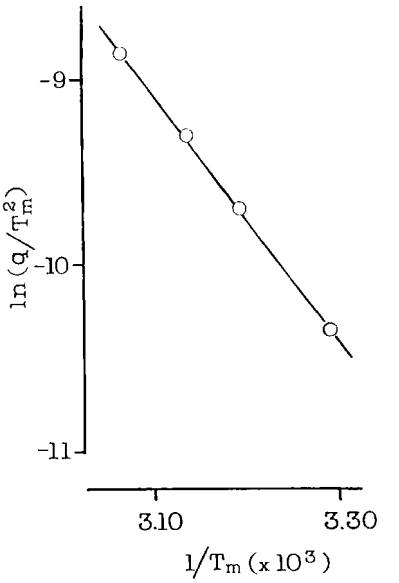

FIGURE 4
Dehydration kinetics of PVP XL: Kissinger plot from DSC data (open pan; 3, 6, 10, and 15 K min^{-1}).

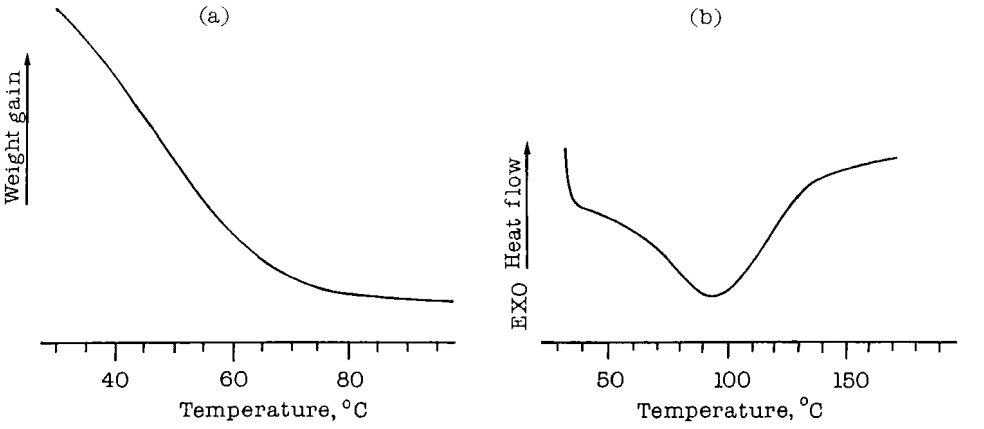

FIGURE 5

TGA (a) and DSC (b) curves recorded at 10 K min^{-1} for the 250-180 μm cross-linked polyvinylpyrrolidone (PVP XL) granulometric fraction (equilibrium moisture content 11.6%, 25 °C).

TABLE 2

Equilibrium Moisture Content (EMC) of Cross-linked Polyvinylpyrrolidone (PVP XL) Granulometric Fractions at Room Temperature and Constant Relative Humidity (RH) Grades.

Granulometric fraction (μm)	Equilibrium moisture content (g_{H_2O}/100 g)			
	40% RH	54% RH	75% RH	97% RH
125-63	11.9	16.9	22.7	31.5
180-125	12.0	16.3	22.7	31.5
250-180	11.6	17.0	22.2	31.0

TABLE 3

Kinetic Parameters of Cross-linked Polyvinylpyrrolidone (PVP XL) Dehydration for the (a) 125-63 μm, (b) 180-125 μm, and (c) 250-180 μm Granulometric Fractions at Various Equilibrium Moisture Content (EMC) from TGA Non-isothermal Data (25 to 150 °C, 10 K min^{-1}).

EMC of PVP XL (g_{H_2O}/100 g)			Reaction order, n (Standard deviation in parentheses, 4 runs)			Activation energy (kJ mol^{-1})		
(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
11.9	12.0	11.6	1.0(.1)	1.2(.4)	1.2(.3)	47.7(0.6)	48.2(1.0)	49.2(1.8)
16.9	16.3	17.0	1.1(.1)	1.1(.1)	1.2(.2)	46.8(2.6)	45.0(1.8)	48.6(2.1)
22.7	22.7	22.2	1.1 (.1)	1.1 (.1)	1.1(.1)	53.1(0.7)	52.2(1.2)	51.3(2.1)
31.5	31.5	31.0	0.8(.03)	0.8(.01)	0.8(.03)	47.3(1.4)	47.8(2.3)	49.1(2.0)

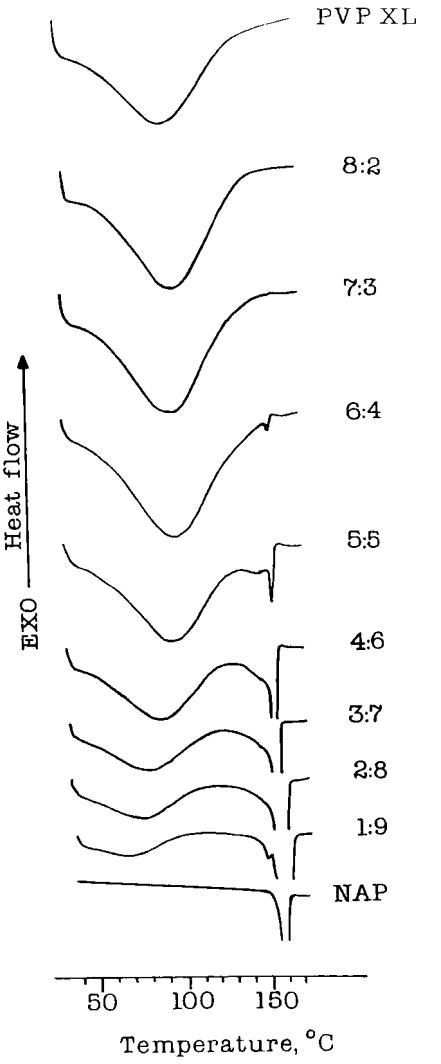

FIGURE 6
DSC curves of cross-linked polyvinylpyrrolidone (PVP XL) (125-63 μm granulometric fraction, equilibrium moisture content 11.9% at 25 °C, $\Delta_{dehydr.}H$ = 350 J g^{-1}), naproxen (NAP) (125-63 μm granulometric fraction, T_f = 156.2 °C, Δ_fH = 135 J g^{-1}), and PVP XL/NAP (*g/g*) blends.

TABLE 4

Thermodynamic and Kinetic Parameters(*) of Cross-linked Polyvinylpyrrolidone (PVP XL) Dehydration in Blends with Naproxen (NAP) from DSC Non-isothermal Data (25 to 175 °C, 10 K min^{-1}).

Blend Composition PVPXL/NAP (*g/g*)	PVP XL Dehydration		
	T_{peak} (°C)[a]	$\Delta_{dehydr.}H$ (J g^{-1})[b]	E_{act} (kJ mol^{-1})[c]
9:1	100	303	58
8:2	102	287	59
7:3	97	317	60
6:4	100	335	60
5:5	96	253	56
4:6	90	253	54
3:7	81	279	56
2:8	77	259	68
1:9	70	268	-

(*) Coefficient of variation (4 runs): a) ≤ 1%; b) ≤ 3%; c) ≤ 6%.

energies calculated from the slopes of the lines were E_{act} = 66.9 kJ mol^{-1} and E_{act} = 49.1 kJ mol^{-1} for heating rates of 1 and 2 K min^{-1}, respectively (Fig. 3b).

The activation energy for the dehydration of PVP XL was also estimated [6] from DSC runs using the Kissinger equation [12]:

$$\ln(q/T_m^2) = - E_{act}/R\,T_m + \text{Const.}, \quad (9)$$

T_m being the peak temperature of the DSC dehydration curve. The reciprocals of T_m at the heating rates q = 3, 6, 10, and 15 K min^{-1} were plotted *vs* $\ln(q/T_m^2)$ and a straight line was obtained (Fig. 4) whose slope gave the activation energy of PVP XL dehydration (E_{act} = 54.4 kJ mol^{-1}).

RESULTS AND DISCUSSION

The thermal behaviour of PVP XL is that expected for hygroscopic amorphous materials (Fig. 5). The EMC values of PVP XL samples equilibrated at 40%, 54%, 75% and 97% relative humidity at a controlled room temperature (25 °C±2 °C) are similar for the three granulometric fractions tested (Table 2).

The kinetic parameters of PVP XL dehydration in Table 3 were calculated processing the TGA data with the "TG KINETIC" programme which is based on the model equation of Wilhelmy, i.e. reaction rate as a function of conversion α and every conversion differential dα corresponding to a proportional mass change dm [13].

Two-way ANOVA (SIPHAR® package, Simed, Creteil Cedex, France) showed that no significant differences exist between the E_{act} values of various granulometric fractions of PVP XL samples with the same EMC. Instead, a significant difference ($P < 0.01$) was found between the E_{act} values of the 125-63 μm and 180-125 μm granulometric fractions equilibrated at different RH conditions. The kinetic parameters of PVP XL dehydration were also calculated processing the DSC data with the "DSC KINETIC" programme (see Experimental), which is based on the same model equation as the "TG KINETIC" one assuming that every conversion differential dα corresponds to a proportional enthalpy change dH [13]. The results are similar to those obtained from TGA experiments (see Table 3), with the exception of the E_{act} = 61.2 kJ mol^{-1} value

found for the PVP XL samples equilibrated at 97% RH, i.e. with the highest EMC. As a general feature of the "DSC KINETIC" programme, the higher the EMC of PVP XL sample, the higher the E_{act} value obtained.

DSC experiments carried out on blends containing about 2.000 mg of PVP XL (125-63 μm granulometric fraction, EMC 11.9%) and the amounts of NAP (125-63 μm granulometric fraction) needed to obtain the weight fractions shown on the respective DSC curves, gave the results presented in Fig. 6. The relevant thermodynamic and kinetic parameters of PVP XL dehydration are given in Table 4. The peak temperature of the dehydration endotherm in blends containing up to 40% NAP keeps close to that of the polymer alone, whilst at higher drug contents it is lowered. This decrease is a function of the composition of the mixture. The dehydration enthalpy of PVP XL ($\Delta_{dehydr.}H$ = 350 J g^{-1}) is seen to be decreased by the presence of the drug, whilst the activation energy of the dehydration process is noticeably increased. The activation energy of mixtures has an average value of 58.9 kJ mol^{-1}, which has to be compared with that of 48.4 kJ mol^{-1} found for PVP XL alone. Thus the crystalline drug somehow hinders the water evolution from the amorphous polymer.

CONCLUSIONS

The characterisation of pharmaceutical materials for quality control purposes is generally accomplished by means of a variety of methods. In this respect thermal analysis has rapidly gained importance as a routine instrumental method for obtaining quantitative predictions on the stability of drugs, excipients, or their mixtures [14]. Results previously reported clearly show that the dehydration of PVP XL follows a first-order kinetics when examined through isothermal (or non-isothermal at low heating rate) TGA [6]. On the other hand, TGA at higher heating rates leads to somewhat lower E_{act} values (25-30%). This discrepancy has been ascribed to an intrinsic inability of dynamic methods to determine correctly activation energies [15]. Underestimates of activation energies by as much as 10 to 25% may occur [16]. In any case, E_{act} of PVP XL dehydration is low, i.e. the rate of water evolution depends on temperature only to a limited extent. From a pharmaceutical point of view it must be stressed that modern instruments are equipped with built-in software programmes to be used with non-isothermal TGA or DSC methods. In our case, activation energy values in the 43 to 54 kJ mol^{-1} (TGA) and 48 to 61 kJ mol^{-1} (DSC) ranges were obtained for PVP XL samples. While the weight fraction of water present may influence the activation energy of the dehydration process, the particle size of PVP XL in the 250 μm to 65 μm range seems not to affect this parameter. Although no ultimate conclusions can be drawn on the reaction mechanism simply by fitting experimental data to any of the mathematical models reported in Table 1, the low energy of interaction between water and PVP XL suggests that such an interaction can be mainly ascribed to surface phenomena. The PVP XL particles present a characteristic popcorn-like structure and appear to be fused into large agglomerates [17]. The similar EMC and E_{act} values for different granulometric fractions can be explained assuming that water is mainly entrapped within the PVP XL pores, i.e. interacts at the intraparticulate rather than external surface level. The influence of NAP on the thermodynamic and kinetic parameters of PVP XL dehydration (i.e. on the energetics of water associated with the polymer and the rate of water evolution from it) suggests that analogous surface phenomena are probably involved in the solid-state interaction between the amorphous polymer and the crystalline drug. This interactional phenomenon which can be seen in Fig. 6, is the grinding induced modification of the melting peak of NAP. We have reported on this observation previously [18].

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